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Simple chemoenzymatic access to enantiopure pharmacologically interesting (*R*)-2-hydroxypropiophenones

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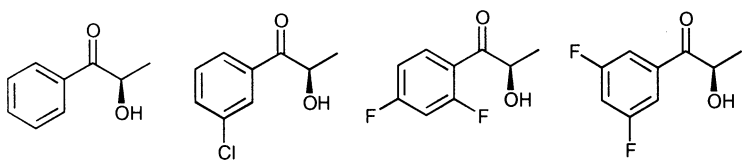
Abstract—A chemoenzymatic synthesis of pharmacological interesting (*R*)-2-hydroxypropiophenones starting from propiophenone derivatives is described. Manganese(III) acetate-mediated acetoxylation followed by fungus-mediated hydrolysis of propiophenone derivatives affords (*R*)-2-hydroxypropiophenones in high enantiomeric excess.

1. Introduction

Chiral α-hydroxy ketones are an important structural unit in many biologically active natural products and they are also important synthons for the asymmetric synthesis of natural products.[1] As such, several chemical methods have been developed for the preparation of optically active α-hydroxy ketones.[1] They are also prepared enzymatically by reduction of the corresponding α-diketone with baker's yeast or an enzymatic kinetic resolution of the racemate of either 2-peroxo-, 2-hydroxy- or 2-acetoxy ketones.[2]

The hydroxy ketones **1a**–**1d** are key intermediates for the synthesis of the pharmacologically interesting 2-HPP derivatives, (*R*)-1-(3-chlorophenyl)-2-hydroxypropan-1-one **1b**, starting material for Bupropion (active ingredient of Wellbutrin® (Glaxo Wellcome) marketed for the treatment of depression, it has also been approved as an aid to smoking cessation under the brand name of Zyban® (Glaxo Wellcome),[3] (*R*)-1-(2,4-difluorophenyl)-2-hydroxypropan-1-one **1c**, a starting material for Ro 09-3355[4] and SM 8668/Sch 39304 (anti-fungal agents)[5] and (*R*)-1-(3,5-difluorophenyl)-2-hydroxypropan-1-one **1d**, a starting material for 1555U88 (an anti-depressant agent and selective inhibitor of norepinephrine uptake).[6] These hydroxy ketones have been obtained in enantiomerically pure form from via the chromatographic separation of enantiomers,[5a] the kinetic resolution of racemic hydroxy ketones,[5c] synthesis from chiral arylepoxides,[5e] by asymmetric α-hydroxylation using oxaziridine methodology,[5d] metal salt-induced α-hydroxylation of ketones,[5b] Sharpless asymmetric dihydroxylation of the silylenolether of the corresponding ketone[3] and the recently reported benzaldehyde lyase-catalyzed carboligation of aromatic aldehydes with acetaldehyde.[7]



1a **1b** **1c** **1d**

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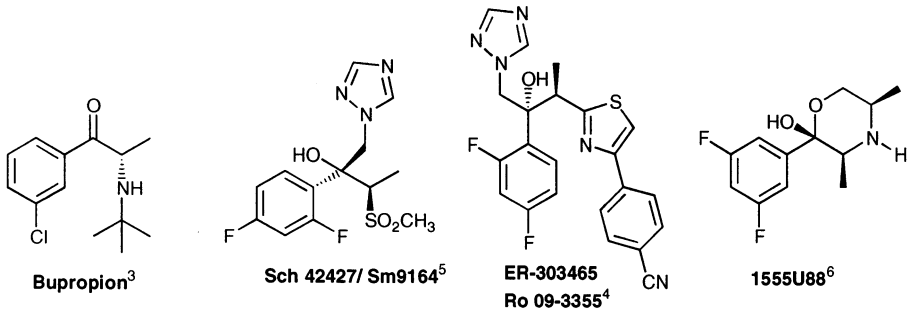
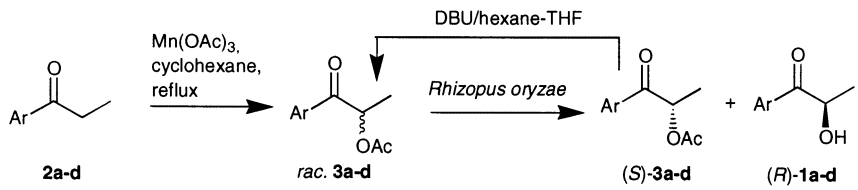


In our ongoing works we have published several papers about the $Mn(OAc)_3$-mediated direct acetoxylation and acyloxylation (carried out via metathesis of the acetic acid by various carboxylic acids) of enones and aromatic ketones[8] followed by the enzymatic- and fungus-mediated resolution of acyloxy enones to obtain optically pure α-hydroxy ketones.[9] In the light of these works, we report herein a simple and efficient chemoenzymatic route to the pharmacological interesting 2-hydroxypropiophenones **1a**–**1d**.

2. Results and discussion

In an initial reaction (Scheme 1), the oxidation of ketones **2a**–**2d** with four equivalents of manganese(III) acetate in cyclohexane furnished the desired α-acetoxy ketones **3a**–**3d** in 83–87% yields after purification by column chromatography. For high yield formation of the acetoxy ketones, the manganese(III) acetate must be dried prior to use. The use of benzene as a solvent also furnished the acetoxy ketones in 76–81% yields with some side products. The direct synthesis of acyloxy ketones from ketones using manganese(III) acetate is an attractive alternative to the other (multistep) procedures. Based on the preliminary information available to us from our previous work with fungus-mediated reactions, a series of fungi were screened for the enantioselective hydrolysis of acetoxy ketones **3a**–**3d** and two of them gave the desired results (*Rhizopus oryzae* (W&P G) and *Rhizopus oryzae* (NRRL 395) Table 1). The bioconversion was performed in DMSO and fungus were incubated in the presence of the α-acetoxy ketone at 30°C. The optimum pH of the reaction medium was found to be 6.0–6.5 and the conversions were monitored by TLC and LC–MS (equipped with a chiral column using authentic hydroxy ketone as reference).[10a] After about 45–50% conversion, the products were separated using flash column chromatography, and the hydroxy ketone products **1a**–**1d** were isolated in 40–46% yields with e.e.s of 88 to >99%. Small quantities of diol were also detected in the crude products by GC–MS. The configuration of the hydroxy ketones was assessed by all products as (*R*) by comparison of its specific rotation with literature data (Table 1). Under these conditions less discrimination was observed using substituted acetoxy ketones **3b**–**3d**. Under similar conditions termination of the reaction after 38–40% con-



Scheme 1.

Table 1. Fungus-mediated hydrolysis of esters

Entry	Substrate	Fungus	Reaction time (h)[a]	(*R*)-Alcohol	% e.e.[b]	% yield
1	**3a**	*Rhizopus oryzae* (W&P G)[c]	48	**1a**	92	46
2	**3a**	*Rhizopus oryzae* (NRRL 395)	60	**1a**	>99	42
3	**3b**	*Rhizopus oryzae* (W&P G)[c]	64	**1b**	94	39
4	**3b**	*Rhizopus oryzae* (NRRL 395)	72	**1b**	>99	40
5	**3c**	*Rhizopus oryzae* (W&P G)[c]	76	**1c**	96	36
6	**3c**	*Rhizopus oryzae* (NRRL 395)	92	**1c**	>99	37
7	**3d**	*Rhizopus oryzae* (W&P G)[c]	72	**1d**	96	35
8	**3d**	*Rhizopus oryzae* (NRRL 395)	96	**1d**	97	34

[a] For 38–40% conversions of **1b**–**1d**.

[b] Enantiomeric excess of **1a**–**1d** was determined by chiral phase HPLC analysis (Chiralpak AD column, UV detection at 254 nm, eluent: *iso*-hexane/2-propanol = 9:1, flow 0.80 mL min^{-1} 20°C, using racemic compounds as references.[10a]

[c] *Rhizopus oryzae* (Went&Prinsen Geerlings, TUBITAK-72465) the culture was obtained from the Marmara Research Center of Turkish Scientific and Technical Research Council.

version increases the e.e. to 96 to >99% for **1b**–**1d** (Table 1). The fungi examined gave comparable results but with *Rhizopus oryzae* (W&P G) the conversion was faster and less selective than that seen with *Rhizopus oryzae* (NRRL 395). Slow conversion was observed with the 2,4-difluoro-substituted derivative **3d**. The hydroxy ketones **1a**–**1d** are stable only when kept in a cold place under an inert atmosphere and away from light. The impure acetoxy ketones obtained after bioconversion, can be epimerized using DBU in hexane/THF[10b] to afford the racemic acetoxy ketones in 81–84% yields after purification by column chromatography. The recycling of the ester makes this method for the enantioselective synthesis of hydroxy ketones quite efficient.

3. Conclusions

The results show that manganese(III) acetate-mediated acetoxylation of ketones followed by fungus-mediated hydrolysis of the acetoxy group provides hydroxy ketones **1a**–**d**, which are important precursors for pharmacologically interesting compounds, with high enantiomeric excesses and in good yields. The undesired acetoxy ketones are epimerized in good yield and reused. In these conversion reactions the enzymes favor the (*R*)-enantiomers.

4. Experimental

4.1. General methods

NMR spectra were recorded on a Bruker DPX 400. Column chromatography was conducted on silica gel 60 (mesh size 40–63 μm). Enantiomeric excesses were determined by HPLC analysis using a Thermo Quest (TSP) GC–LC–MS equipped with an appropriate optically active column, as described in the footnotes of the corresponding Tables. GC–MS spectra were determined on a phenomenex Zebron ZB-5 capillary column (5% phenylmethylsiloxane). Optical rotations were measured with Bellingham&Stanley P20 polarimeter or with a Perkin–Elmer 241 polarimeter.

4.2. General procedure for synthesis of 2-acetoxy ketones 3

A mixture of manganese(III) acetate (5.36 g, 20 mmol) and the ketone (5 mmol) in cyclohexane (50 mL) was stirred under reflux (the reaction was monitored by TLC) using a Dean–Stark trap. The mixture was cooled to rt, diluted with ethyl acetate and the resulting organic solution washed successively with 1 M aqueous HCl solution, saturated aqueous $NaHCO_3$ solution and brine, and dried over anhydrous $MgSO_4$. The crude product was chromatographed on flash silica gel in 1:3 ethyl acetate–hexane to afford the acetoxy ketone product.

4.3. Representative example for hydrolysis of 2-acetoxy ketones

Rhizopus oryzae was used for the experiments. It was cultivated on boiled rice and the fungal spores were transferred by loopfuls into sterile flasks containing the medium and grown in rotary shaker at 30°C for 2 days. The medium for fungal growth included glucose syrup (15.0 g), $(NH_4)_2SO_4$ (1.0 g), KH_2PO_4 (0.30 g), $MgSO_4$ (0.12 g) and $ZnSO_4$ (0.02 g) diluted to 500 mL with distilled water. The medium was divided into five and sterilized in an autoclave for 15 minutes. Spores from the main plate were transferred into an Erlenmeyer flask containing 100 mL sterile medium. The fungus was inoculated at 30°C for 2 days in the rotary shaker and a solution of the substrate (2 mmol) in DMSO (3 mL) was added (pH 6.0–6.5). Shaking was resumed until approximately 38–42% of the racemic acetate was hydrolyzed. The fungus was removed by filtration, washed with distilled water and the combined aqueous phases extracted with ether. The organic extract was dried, filtered and concentrated and the alcohol and unhydrolyzed acetate were then separated by flash column chromatography (EtOAc:hexane, 1:2).

4.4. 2-Acetoxy-1-phenylpropan-1-one 3a[9a]

Yellow oil; yield: 84 mg (87%). IR(TF): 1740, 1700 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.88$–7.92 (m, 2H), 7.41–7.60 (m, 3H), 5.86 (q, $J = 7.0$ Hz, 1H), 2.03 (s, 3H), 1.59 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 201.8$, 171.3, 134.2, 133.9, 128.8, 128.5, 84.2, 20.2, 17.4.

4.5. 2-Acetoxy-1-(3-chlorophenyl)-propan-1-one 3b

Viscous oil; yield: 97 mg (86%). IR(TF): 1750, 1710 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.26$–7.44 (m, 2H), 7.78–7.88 (m, 2H), 5.78 (q, $J = 6.9$ Hz, 1H), 2.10 (s, 3H), 1.59 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 198.4$, 171.8, 134.7, 133.6, 130.4, 130.2, 129.3, 126.8, 83.9, 21.1, 17.7. Anal. calcd for $C_{11}H_{11}ClO_3$(226.6): C, 58.29; H, 4.89. Found: C, 58.48; H, 4.92%.

4.6. 2-Acetoxy-1-(2,4-difluorophenyl)-propan-1-one 3c[5f]

Yellow oil; yield: 97 mg (85%). IR(TF): 1760, 1710 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.93$–8.03 (m, 1H), 6.82–7.14 (m, 2H), 5.84 (m, 1H), 2.03 (s, 3H), 1.62 (d, $J = 6.8$ Hz, 3H).

4.7. 2-Acetoxy-1-(3,5-diflurophenyl)-propan-1-one 3d

Yellow oil; yield: 95 mg (83%). IR(TF): 1750, 1710 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.76$–8.15 (m, 1H), 6.74–7.32 (m, 2H), 5.80 (m, 1H), 2.01 (s, 3H), 1.58 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 198.9$, 172.3, 165.2 (d, $J = 248$ Hz), 138.2, 112.4, 111.7 (d, $J = 20$ Hz), 109.1 (d, $J = 25$ Hz), 83.9, 20.4, 17.1. Anal. calcd for $C_{11}H_{10}F_2O_3$ (228.2): C, 57.90; H, 4.42. Found: C, 58.12; H, 4.62%.

4.8. (*R*)-2-Hydroxy-1-phenylpropan-1-one 1a

Viscous oil, e.e. >99%; $[\alpha]_D^{22}=+85.3$ (*c* 2.0, $CHCl_3$), [lit.[9a] $[\alpha]_D^{20}=+82.2$ (*c* 2.0, $CHCl_3$) for 96% e.e.; HPLC (Chiralpak AD): R_t (*R*) = 14.3 min, R_t (*S*) = 12.1 min; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.89$–7.92 (m, 2H), 7.40–7.62 (m, 3H), 4.99 (q, $J=6.0$ Hz, 1H), 3.80 (br.s, 1H), 1.41 (d, $J=6.0$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=201.6$, 134.2, 134.0, 128.7, 128.3, 69.2, 22.0.

4.9. (*R*)-1-(3-Chlorophenyl)-2-hydroxypropan-1-one 1b

Viscous oil; e.e. >99%; $[\alpha]_D^{20}=+73.3$ (*c* 1.0, CH_2Cl_2); HPLC (Chiralpak AD): R_t (*R*) = 13.3 min, R_t (*S*) = 11.4 min, ^{1}H NMR ($CDCl_3$): $\delta=7.26$–7.46 and 7.76–7.91 (m, 4H), 4.96 (q, $J=6.9$ Hz, 1H), 3.81 (br.s, 1H), 1.42 (d, $J=6.9$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=197.6$, 134.9, 133.4, 130.3, 130.1, 129.1, 126.8, 70.2, 21.4; Anal. calcd for $C_9H_9O_2Cl$: C, 58.55; H, 4.91%; found: C, 58.26; H, 5.21%.

4.10. (*R*)-1-(2,4-Difluorophenyl)-2-hydroxypropan-1-one 1c[5c,f]

Yellow oil; e.e. = 97%; $[\alpha]_D^{20}=+66.7$ (*c* 1.0, $CHCl_3$), [lit.[5f] $[\alpha]_D^{20}=-67.1$ (*c* 1.0, $CHCl_3$) for >99.5% e.e. (*S*); HPLC (Chiralpak AD): R_t (*R*) = 10.9 min, R_t (*S*) = 8.8 min, ^{1}H NMR ($CDCl_3$): $\delta=7.92$ (m, 1H), 6.82–7.14 (m, 2H), 5.01 (m, 1H), 3.75 (br s, 1H), 1.42 (d, $J=6.6$ Hz, 3H).

4.11. (*R*)-1-(3,5-Difluorophenyl)-2-hydroxypropan-1-one 1d[6]

Viscous oil; e.e. >99%; $[\alpha]_D^{20}=+70.2$ (*c* 1.1, $CHCl_3$); HPLC (Chiralpak AD): R_t (*R*) = 10.8 min, R_t (*S*) = 8.9 min; ^{1}H NMR ($CDCl_3$): $\delta=7.78$–8.17 (m, 1H), 6.71–7.31 (m, 2H), 4.99 (m,1H), 3.36 (br.s, 1H), 1.42 (d, $J=6.7$ Hz, 3H).

Acknowledgements

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